

The first total synthesis of (\pm)-chanoclavine-? acid and an alternative total synthesis of (\pm)-chanoclavine-?

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THE FIRST TOTAL SYNTHESIS OF (±)-CHANOCLAVINE-I ACID AND AN ALTERNATIVE TOTAL SYNTHESIS OF (±)-CHANOCLAVINE-I¹

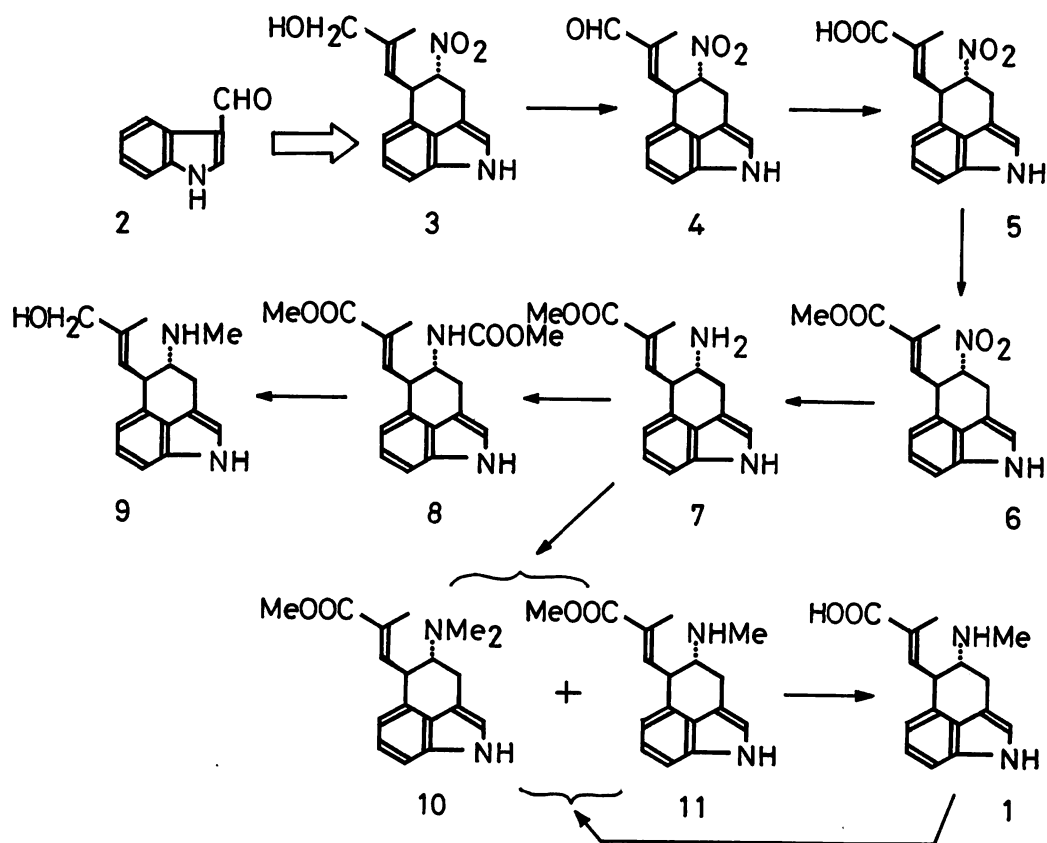
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Abstract ——— The total synthesis of (±)-chanoclavine-I acid was achieved for the first time. An alternative total synthesis of (±)-chanoclavine-I was also reported.

Chanoclavine-I acid (1) is a major alkaloid in the seeds of *Ipomea violacea* and its structure was established by H. R. Shough and co-workers in 1977.² In this communication, we wish to report the first total synthesis of (±)-chanoclavine-I acid and an alternative synthesis of (±)-chanoclavine-I (9).^{3e,i}

In our continuing project for preparing biologically active ergot alkaloid derivatives,³ (E)-4,5-trans-5-(2-hydroxymethyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole (3) is now readily available in five steps in 15% overall yield starting from indole-3-carboxaldehyde (2).^{3e} Therefore, 3 was converted to the aldehyde (4) (mp 186-187°C) in 55% yield by the treatment with pyridinium chlorochromate in methylene chloride. Subsequent oxidation of 4 with sodium hypochlorite in the presence of 2-methyl-2-butene⁴ afforded the corresponding carboxylic acid (5) (mp 264-265°C) in 97% yield. Methylation of 5 with ethereal diazomethane generated 95% yield of the methyl ester (6) (mp 188-189°C), which was then reduced with zinc amalgam and hydrochloric acid to produce the corresponding amine (7) (oil) in 98% yield. Since we have already succeeded in the synthesis of (±)-chanoclavine-I (9),^{3e,i} we attempted to convert 7 to 9 in order not only to confirm its structure but also to establish an alternative synthesis route to 9. Thus, treatment of 7 with methyl chloroformate in the presence of triethylamine produced 67% yield of the corresponding methyl carbamate (8) (oil). Reduction of 8 with lithium aluminum hydride in dry tetrahydrofuran afforded 9 in 95% yield. Various attempts⁵ to obtain chanoclavine-I acid methyl ester (11) by methylating

the amine (7) were made in vain because of the steric hindrance around the amino group. Finally, methylation of 7 with dimethyl sulfate in the presence of potassium carbonate was found to produce the desired 11 (oil) in 25% yield together with 15% yield of the corresponding dimethylamino derivative (10) (mp 141-142°C). Alkaline hydrolysis of 11 in methanol and subsequent column chromatography on Amberlite IRA 120 afforded (±)-chanoclavine-I acid⁶ (1) in 80% yield. Although 1 did not exhibit clear carbonyl absorption band in its ir spectrum, the HCl salt⁷ of 1 showed strong absorption band at 1698cm^{-1} .² For further structural confirmation, methylation of 1 was carried out with ethereal diazomethane to produce 10 and 11 in 7% and 35% yields, respectively. Mass spectral data of 1 and ¹H-nmr spectrum of its HCl salt were identical to those reported in the literature.²



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5. Both Eschweiler-Clark and Leuckart reactions did not work. Attempts to produce imine by the reaction of 7 with various aldehydes were found to be unsuccessful.
6. Colorless powder from ethanol-H₂O. mp 289-290°C (dec.). Ir (KBr) cm⁻¹: 3150, 1607, 1564, 1380, 1084, 760. 400MHz ¹H-nmr (DMSO-d₆) δ: 1.94 (3H, s), 2.37 (3H, s), 2.65 (1H, dd, J=15 and 8 Hz), 2.86 (1H, dt, J=4 and 8 Hz), 3.16 (1H, dd, J=15 and 4 Hz), 3.92 (1H, dd, J=10 and 8 Hz), 6.49 (1H, d, J=7.5 Hz), 6.55 (1H, d, J=10 Hz), 6.98 (1H, t, J=7.5 Hz), 7.01 (1H, s), 7.15 (1H, d, J=7.5 Hz), 10.66 (1H, s, COOH). Ms m/z (%): 270 (M⁺, 100), 252 (8.8), 197 (14.8), 168 (41.3), 167 (8.4), 155 (35.0), 154 (25.7). High resolution ms m/z: Calcd for C₁₆H₁₈N₂O₂: 270.1367. Found: 270.1363.
7. Colorless prisms from ethanol-H₂O. mp 288-289°C (dec.). Ir (KBr) cm⁻¹: 3330, 2920, 1698, 1581, 1445, 1221, 753. 400MHz ¹H-nmr (DMSO-d₆+D₂O) δ: 2.03 (3H, s), 2.65 (3H, s), 3.12 (1H, dd, J=15 and 7 Hz), 3.32 (1H, dd, J=15 and 4 Hz), 3.68 (1H, dt, J=4 and 7 Hz), 4.35 (1H, dd, J=10 and 7 Hz), 6.53 (1H, d, J=10 Hz), 6.68 (1H, d, J=8 Hz), 7.15 (1H, t, J=8 Hz), 7.20 (1H, s), 7.31 (1H, d, J=8 Hz), 10.91 (1H, s, COOH).

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